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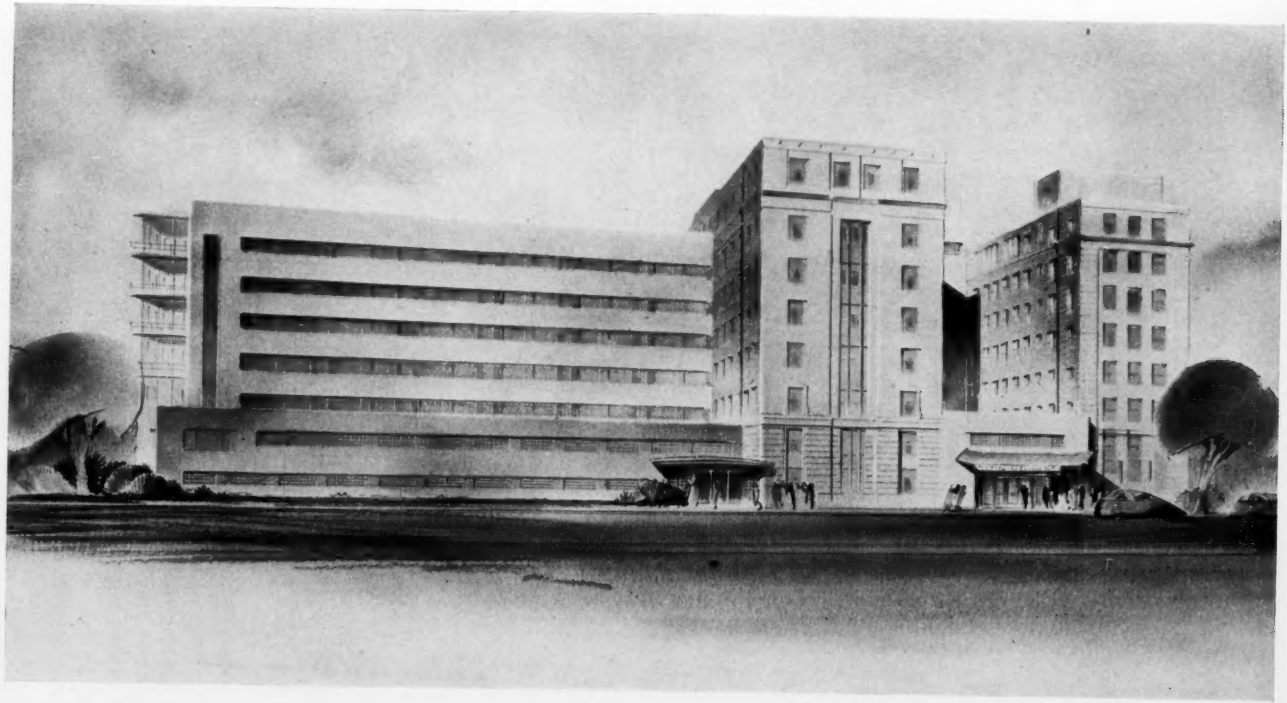

PROPOSED ADDITION TO CLEVELAND CLINIC HOSPITAL

PARTIAL GIGANTISM OF THE FACE WITH NEUROLOGIC COMPLICATIONS

LOUIS J. KARNOSH, M.D., AND W. JAMES GARDNER, M.D.

Although it is a rather rare "embryonic error," congenital unilateral hypertrophy of the tissues of the face has been described in the medical literature at frequent intervals since 1836. Werner[1] in 1905 gave this subject special attention when he reviewed a case of his own and reported his findings on histologic examination of the soft tissues involved in the hypertrophy. A year later Pagenstecher[2] described a patient with this deformity and, on performing a cosmetic operation, found that the enlargement involved not only fat and connective tissues but the salivary glands, the mucous membranes, and even the external maxillary artery and facial nerve.

More recently Rushton[3] pointed out that the structures chiefly affected in partial gigantism of the face are among those derived from the first branchial arch, but other parts may be involved, such as the nostril, the upper jaw, the zygoma, the frontal bone, and the ear. The increased size of the teeth arising from the latter maxillary process in contrast with those developing from the premaxilla is invariably noted in this condition and should aid in differential diagnosis, for no such dental disparity occurs in simple hyperplasia or in tumors.

It is generally agreed that in this disturbance the involvement is never restricted to one type of tissue or to one organ. In a sense partial gigantism of the face is the antithesis of hemiatrophy of the face, and a neurotrophic influence may be present in both. However, Werner[1] emphasized that the hypertrophied regions do not correspond to the distribution of certain nerves or groups of nerves. Sensory disturbances are rarely found, and paralysis of a motor nerve, when it does occur, appears to be secondary to hypertrophy of the soft tissues through which it passes.

In all carefully studied cases it is evident that embryonic dispositions rather than neurotrophic factors are responsible for the overgrowth. The areas of hypertrophy are clearly delineated by the embryonic folds and cleavage lines of the face. The line of demarcation between normal growth and overgrowth is usually established along the fusion zones between the premaxilla and the lateral maxillary process in the upper jaw and in the midline of the lower jaw. Hence dental malformations are

important criteria in establishing the extent and degree of hypertrophy, which will usually be found to involve the teeth, gums, and alveolar bone and all accessory structures in the mucous membranes.

Although such hypertrophy has been known to involve any or all structures of the face on one side, no data are on record indicating that the brain case or its contents may be affected by the abnormal process. No predominantly neuroblastic structure has been incorporated in the description of partial gigantism of the face, although portions of motor nerves passing through the hypertrophied connective tissues, particularly the facial and hypoglossal trunks, have been found to be greatly thickened.

However irregular and variable this anomaly may be, it has always been assumed that the process is entirely a surplus growth in tissues other than those that arise from the neural tube. Hence a patient with partial gigantism of the face who presents symptoms of cerebral complication is not without interest and may indicate that this puzzling congenital disturbance may extend to structures within the skull.

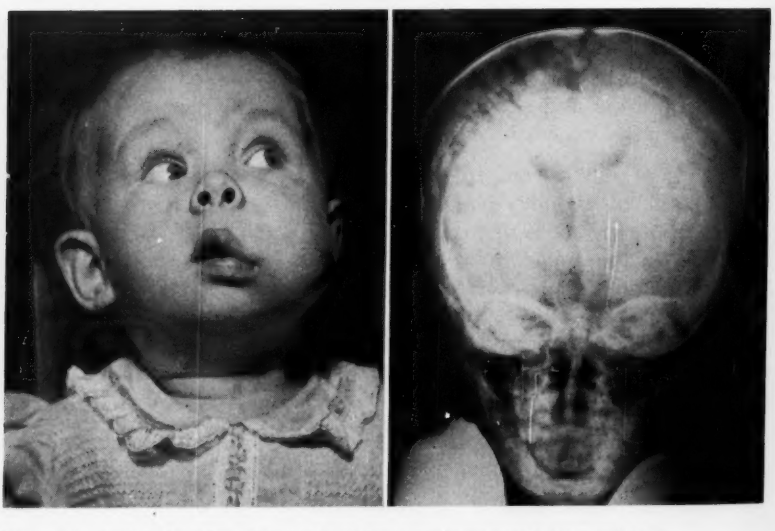

FIG. 1 (a) Partial gigantism of left side of face involving cheek, lips, and jaws.

(b) Pneumoencephalogram showing abnormal angle in vertical midline of skull and face. The filling defect over left hemisphere is more than an artefact and indicates hypertrophy of that side of brain.

CASE REPORT

A baby girl, aged 14½ months, was first examined on August 5, 1944. She was the first-born child of a mother aged 34. Labor was somewhat prolonged, but delivery was accomplished with ease by high forceps. For several minutes the child showed a moderate degree of asphyxia with shallow respirations. The obstetrician immediately observed an obvious deformity of the left cheek and left superior maxilla, which was not the result of instrumentation. This swelling was described as elephantiasis of the cheek.

When the baby was about 3 months old, she had her first episode of unconsciousness and subsequently had twelve to fifteen more. These seizures appeared without warning and lasted from fifteen minutes to an hour; the child became pale, produced a clicking sound from the throat, lost consciousness, and became utterly limp without muscular twitching or stiffening of the limbs. She had frequent bleeding from the left ear and recently bled rather profusely from the mouth when cutting two upper teeth. The teeth on the left side of the jaws erupted much earlier than did those on the right side.

Despite these handicaps the youngster appeared healthy, ate very well, and developed normal toilet habits. However, at 14 months of age she manifested no desire to crawl, stand, walk, or talk. She sat up, played normally with toys, and was rather overactive and somewhat irritable and sensitive to noise. She made no attempt to support herself when propped up in the standing position.

The skull, on examination, showed no gross asymmetry. The head was not enlarged, and the anterior fontanelle was normal in size for her age. Percussion note over the head was not increased. There was a light brown discoloration on the left side of the neck extending from the mastoid area to the supraclavicular level. This was a nevus not unlike that existing in the same area described by Werner.[1]

The left cheek was enormously enlarged (fig. 1a). There was slight enlargement of the left nostril. In the upper lip the overgrowth was restricted to the portion arising from the left lateral maxillary process. The cheek substance was soft and sagged downward. The lower lip showed less pronounced hypertrophy beginning in the midline. The left ear was slightly longer than the right (0.2 cm.), and the contours were slightly irregular.

The contents of the oral cavity showed as prominent an asymmetry as did the face. The left side of the tongue was much thicker, and the papillae were more prominent than were the same structures on the right side.

The teeth and the hard tissues of both upper and lower jaws presented a striking contrast (fig. 2). The midline of the upper jaw appeared to be shifted to the right; the gum tissue was greatly thickened in the areas extending to the left of a clearly marked cleavage line between the lateral incisor and the first bicuspid. Three erupted teeth in the hypertrophied left jaw were definitely larger than the corresponding teeth on the opposite side, and all erupted prematurely. The same asymmetry to a lesser degree was present in all lower teeth and peridental structures in the lower jaw beginning in the midline.

Neurologic examination did not disclose elements of particular value in establishing cause for the attacks of unconsciousness or the delay in standing and walking. The eyeballs appeared equal in size; the pupils were equal and reacted to light and distance. There was a tendency to bilateral internal squint. Glimpses of the eyegrounds were obtained, and these were quite clear. Corneal reflexes were normally intact.

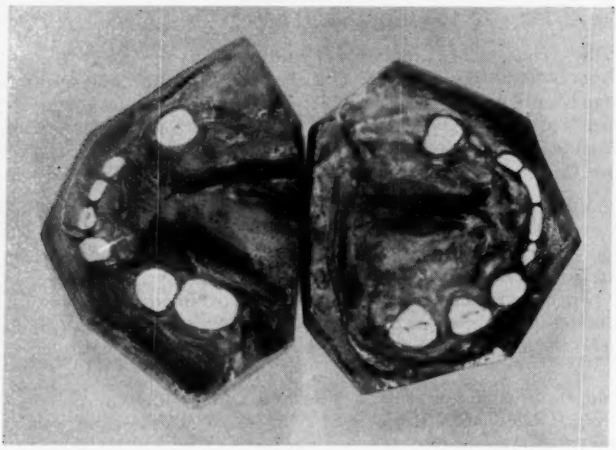

FIG. 2 Plaster casts of upper and lower jaws showing general overgrowth of teeth, gums, and jaws in left lateral maxillary and mandibular embryonic processes. (Courtesy of Dr. Charles A. Resch.)

The zygomatic branches of the left facial nerve, which passed through the substance of the enlarged left cheek, were paralyzed. The left angle of the mouth sagged, and grimacing movements of this part of the face were entirely absent. The facial muscles about the eyes were bilaterally active.

Hearing tests could not be accurately performed. The child gave no evidence of difficulty in swallowing. Tongue movements appeared normal.

Deep tendon reflexes were normally present and active in all extremities. No pathologic reactions could be elicited. There was no evidence of spastic or flaccid weakness in the lower extremities which would explain the child's indisposition to learning to walk.

Roentgenographic and pneumoencephalographic studies were made (fig. 1b).* Most striking was the angle between the vertical anteroposterior midline plane of the brain case and the same plane of the face. The asymmetry of the facial bones was not pronounced, probably because bone density was not greatly increased on the hypertrophied side.

Of particular interest to the neurologist was the evidence of asymmetry of the cranial contents. Air studies showed the left lateral ventricle to be elevated and both ventricles shifted to the right. Over the entire left hemisphere was a filling defect in definite contrast to the normal air spaces outlining the right hemisphere. These findings were subject to several interpretations, among which could be included the idea that the left cerebral hemisphere was part of the congenital partial gigantism.

Electroencephalographic studies were made in an attempt to classify the seizures of unconsciousness in terms of epileptic variants. Bipolar recordings were made over six regions of the scalp. The record showed an almost continuous two to three per second

* Courtesy of Dr. J. E. McClelland, University Hospitals, Cleveland.

activity. Some of these slow waves alternated with a rapid spike not unlike discharges observed in petit mal epilepsy and were bilaterally synchronous, indicating that the abnormality was subcortical and not due to a local cortical lesion.

SUMMARY

The patient had partial gigantism of the face. Roentgenography, pneumoencephalography, and electroencephalography indicated that the ipsilateral cerebral hemisphere was also involved. From a purely clinical standpoint it is difficult to correlate the attacks of unconsciousness and the delay in walking with unilateral cerebral hypertrophy. However, there is no reason to believe that such asymmetry must present unilateral neurologic defects or a focal form of epilepsy.

The pigmented nevus on the neck is suggestive and is emphasized in the consideration of the child's seizures, because the cerebrum may be the site of the angioma.

Treatment of partial gigantism of the face is almost entirely a problem for the plastic surgeon. Pagenstecher's[2] experience with surgery has not been very encouraging. His patient had a resection of some of the fatty tissue of the cheek at 3 years of age. Hypertrophy recurred and even became worse. Another operation at the age of 35 revealed huge overgrowth of the parotid gland and duct, blood vessels, skin, fatty and connective tissue, and local nerve trunks. Resection of nonessential tissue and a large part of the zygomatic bone produced only a slightly satisfactory cosmetic effect. The treatment of the facial nerve palsy is an even more insurmountable problem, because any nerve transplant from another source is likely to be affected by the peculiar local factor, which distorts all tissues in the vulnerable area. Whatever the surplus growth factor may be in partial gigantism of the face, it is evident that its activity is sharply restricted by definite embryonic zones.

If it is true that partial facial hypertrophy may be associated with partial brain hypertrophy, then it can be said that the neurologist has a new syndrome for which no rational treatment exists at present. Neurosurgery will be indicated only if and when intracranial tension is increased and progressive brain symptoms make their appearance.

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TREATMENT OF WOUNDS

GEORGE CRILE, JR.

There can be no standard treatment for wounds. The treatment of each wound must be individualized, taking into account such factors as destruction of tissue, amount of contamination, and lapse of time since the wound was received. The final decision as to the treatment of a wound must be based on sound knowledge of the physiology and pathology of the healing process.

The chief factors that promote sound and rapid wound healing are as follows:

1. Absence of infection
2. Absence of foreign material
3. Good blood supply
4. Complete immobilization
5. Pressure dressing
6. Normal serum proteins
7. Normal supply of vitamin C
8. Absence of nerve injuries, debilitating disease, and unrecognized factors that may retard healing

BACTERIOLOGY

The staphylococcus is one of the most common contaminants of wounds. This organism is widely distributed in the skin, in the nose and throat, and often even in the air.

Staphylococcic infections are characterized by suppuration. Thick creamy pus forms early, and in the average case the infection remains more or less localized. When the organisms are of high virulence (usually hemolytic Staphylococcus aureus) or when the patient's resistance is low, the staphylococcus may become more invasive and is likely to cause spreading cellulitis, lymphangitis, or septicemia. But most staphylococcic infections of wounds are low grade and often cause protracted suppuration and drainage.

Before the advent of the sulfonamides, hemolytic streptococcus was the most dreaded cause of fulminating infection. Infections from this organism have been known to produce septicemia and death within a day or two of onset. A rapidly spreading cellulitis, lymphangitis, or septicemia, often accompanied by chills and fever, is characteristic of virulent infection with hemolytic streptococcus. The pus is likely to be

thin, brownish or reddish in color due to hemolysis of blood cells, and relatively scanty in comparison with the amount of cellulitis. In its less virulent forms, or when the resistance of the patient is high, the hemolytic streptococcus may cause persistent suppuration.

Nonhemolytic streptococci and Bacillus coli predominate in the gastrointestinal tract and are the most common contaminants of penetrating wounds of the abdomen. These organisms are of relatively low virulence, do not invade the tissues extensively, and cause relatively little cellulitis or lymphangitis. They rarely cause septicemia. The most common infection by these organisms is localized suppuration. The pus may vary in consistency and color from thin and brown to thick and white; if B. coli is present, the pus has a characteristic foul odor.

B. pyocyaneous causes superficial, usually nonpathogenic infections characterized by the production of green pus. Except for delaying wound healing and interfering with skin grafting, this type of infection is of little clinical significance.

Mixed infections, in which several or all of these organisms may be present, may occur and are unpredictable in their course.

SOURCES OF CONTAMINATION

Most wounds are contaminated not so much by the instruments which inflict them as by subsequent exposure to virulent bacteria. An instrument which inflicts a wound, although far from sterile, is not likely to be contaminated with virulent organisms unless it has been in contact with infected material, such as a knife blade used in operating in a case of infection. Pocket knives, kitchen utensils, tools, and so forth, even if dirty, are not too dangerous a source of infection provided that the wounds they inflict are protected from further contamination. The resistance of the tissues is high when a wound is inflicted by a sharp instrument that does not traumatize and devitalize tissues.

The reaction to nonmetallic foreign bodies is more severe than is that to most metals, and infection is likely to occur. Infection introduced by these missiles is not likely to be virulent unless the wound is further contaminated by ill guided attempts at treatment.

The most virulent organisms that commonly infect wounds come from the nose and throat of the patient or his attendants. These organisms, hemolytic streptococcus, staphylococcus, and various other pathogens, are easily transferred to the wound from the nose and throat or from the hands of the attendants. For this reason the wound should

be protected as early as possible with a sterile or at least a clean covering to prevent contamination with virulent organisms. Definitive treatment should be deferred until sterile gloves, masks, and instruments are available.

A serious and common error made by the layman is to wrap a fresh wound in a handkerchief or to suck it. There is no single way to infect a wound more seriously than to expose it to the contamination of the mouth or of a used handkerchief. A piece of shirt tail or any piece of clothing which is not grossly dirty makes a suitable emergency covering for a wound until sterile dressings are available. The most important thing is to cover the wound so that it will not become contaminated by organisms from the nose, throat, or hands of the patient or his attendants.

The air contains organisms which, although generally of low virulence, will contaminate a wound and cause infection. This is particularly true in crowded places and when upper respiratory tract infections are prevalent. It is important that a wound be protected as soon as possible from contamination by organisms in the air.

Penetrating wounds of the abdomen or wounds around the rectum may be contaminated by B. coli or other organisms from the gastrointestinal tract. Little can be done to prevent such contamination, but adequate drainage should be provided for the infection which ensues.

PREVENTION OF INFECTION

Second in importance only to protecting a wound from contamination is prompt and adequate chemotherapy. Sulfonamides and penicillin effectively control infections due to hemolytic streptococcus and staphylococcus, which constitute the most common and severe pyogenic infections. If a chemotherapeutic drug is not introduced directly into the wound, systemic chemotherapy should be instituted at once.

If the wound is severe or possibly contaminated, the dissemination of the infection can be best prevented by immobilizing the affected part by application of a splint or a plaster cast. The spread of infection though the lymphatics is thereby controlled, and infection, should it occur, tends to remain localized.

Pressure dressings are of value in combating infection: They not only obliterate the dead space, which would otherwise fill up with serum or air, but also approximate the tissues and allow normal healing to take place. Cavities filled with blood or serum have an increased tendency to become infected, and if accumulation of serum can be prevented, the incidence of infection will be lowered.

TREATMENT OF ESTABLISHED INFECTION

Chemotherapy. The new chemotherapy, the sulfonamides and penicillin, has largely replaced the antiseptic therapy of the last decade. It has long been realized that older types of antiseptic when introduced into wounds in concentrations sufficiently high to destroy bacteria also destroy tissue cells. This destruction of tissue does more harm than the antiseptic action of the drugs does good.

Sulfonamides. The sulfonamides, and more recently penicillin, do not have the disadvantage of destroying sensitive tissue cells. At the same time their bacteriostatic and bactericidal properties render them effective in the prevention and control of infection from many common pyogenic organisms. Whether the efficacy of these products will prove to be higher when introduced directly into the wound than when given systemically is still debatable. Most well controlled experiments on animals indicate that the protective and therapeutic value of these products is no higher when used locally than when used systemically. The occurrence of this phenomenon in sulfonamide therapy is explained by the fact that the action of sulfonamides is inhibited by pus, necrotic tissue, or products of proteolysis. It is established beyond a doubt, however, that sulfonamides, whether given locally or systemically, do prevent the invasion of tissue by organisms sensitive to their activity.

Hemolytic streptococcus is specifically controlled by sulfonamide therapy. To a lesser degree staphylococcus is controlled by sulfathiazole and sulfadiazine as well as by high concentrations of sulfanilamide. Even nonhemolytic streptococcus and B. coli appear to be somewhat inhibited by high concentrations of these drugs.

Sulfathiazole, and to a lesser degree sulfadiazine, is irritating to tissues. Sulfanilamide causes little irritation and is absorbed rapidly and completely. Probably the rate of absorption as well as the amount of tissue reaction caused by these drugs is an expression of their solubility. Sulfanilamide, which is more soluble, is absorbed so rapidly that extremely high concentrations of the drug are obtained in the tissues. When the concentration of sulfanilamide rises, the staphylococcus, which is not susceptible to sulfanilamide levels obtained by systemic administration, is also amenable to control. In view of this fact, and since the more soluble sulfanilamide does not tend to cake in tissues or cause excessive foreign body reaction, sulfanilamide would seem to be preferable for local application. Those who favor sulfathiazole state that foreign body reaction and tendency to cake are minimal when sulfathiazole

is prepared in microcrystalline form[1] and are enthusiastic about the results. In all probability there is little difference between the efficacy of the two drugs used locally, or between results obtained by the local use of these drugs and those obtained by systemic administration of full doses of either sulfathiazole or sulfadiazine.

When sulfanilamide is introduced into the peritoneal cavity, absorption is extremely rapid, and high blood levels may be expected; the same results are obtained to a lesser extent when the drug is introduced into the pleural cavity. The level of sulfanilamide in the blood rises approximately 1 mg. per 100 cc. for every gram of powder introduced into the peritoneal cavity. Thus, if 10 Gm. is used, a blood level of approximately 10 mg. per 100 cc. may be expected.

When sulfonamides are applied to freshly burned surfaces, similar rapid absorption into the blood takes place, but when sulfonamides are introduced into a wound or are applied to granulating surfaces, the process is much slower, and there need be no fear of overabsorption.

Since the effects of the sulfonamides are neutralized by peptones and products of proteolysis, sulfonamide therapy is obviously no substitute for prompt and adequate drainage of abscesses or pockets of pus. Azochloramid, however, has a specific effect in neutralizing products of proteolysis and thereby facilitates the activity of sulfonamides. The effect of azochloramid and sulfanilamide used together is better than that of either of the drugs used independently.

One objection to the local use of sulfonamides is the tendency for the drugs, when applied locally, to sensitize the patient to their subsequent use. Oral administration of sulfonamides rarely induces sensitivity, but evidence is accumulating to indicate that topical application often induces both local and systemic sensitivity. The routine use of sulfonamides in the local treatment of minor cuts and burns must be evaluated in the light of this possibility.

Penicillin. The clinical action of penicillin is identical with that of the sulfonamides and is more effective. Organisms that are susceptible to sulfonamide therapy respond even better to treatment with penicillin. Again hemolytic streptococcus is the most sensitive, staphylococcus is somewhat less sensitive, and nonhemolytic streptococcus and B. coli are only slightly susceptible to control. Penicillin should promptly and completely control cellulitis or lymphangitis due to the hemolytic streptococcus or staphylococcus but will have little effect on mixed flora in peritonitis resulting from a ruptured appendix. Penicillin is not a sub-

stitute for surgical drainage of pus, and although occasionally it will sterilize cavities filled with pus or clear up infection when drainage is inadequate, it cannot be counted on to do so.

Like the sulfonamides, penicillin will control cellulitis around an abscess and will diminish the systemic reaction to infection. Even in such mixed infections as ulcerative colitis and pulmonary suppuration the systemic reaction is often partially controlled when penicillin is given. But the underlying disease condition, whether it be an undrained abscess, empyema, or an ulcerative lesion of the bowel, is rarely affected by the administration of the drug.

The advent of penicillin has not widened the field of chemotherapy but has merely rendered it more fertile. Penicillin does just what sulfadiazine does, but it does it better.

Penicillin is ineffective when given by mouth and must be given either intramuscularly or intravenously. The drug is excreted rapidly by the kidneys and hence should be given in small divided doses rather than in single large ones. If the drug is given intramuscularly, the absorption is slower, and satisfactory levels are maintained in the blood for a longer time than when the same dose is given intravenously. An alternative method is the continuous intravenous drip.

The average daily dose of penicillin for controlling infections of moderate severity due to the hemolytic streptococcus or staphylococcus is 90,000 units given intramuscularly, 15,000 units every four hours day and night. If the infection is susceptible to control with penicillin, it will show definite evidence of improvement within twelve to forty-eight hours. If no improvement is noted in three days, improvement probably will not occur, no matter how long the drug is given. The average course of penicillin therapy lasts four days. Relapses may occur, just as they do with sulfonamide therapy, if treatment is discontinued too soon. In severe infections it is often well to continue to give small amounts (30,000 units daily) for several days to prevent such relapses.

In fulminating infections or in infections caused by organisms not susceptible to penicillin therapy, larger doses, up to 300,000 units daily, may be given by continuous intravenous drip. Lyons[2] believes it is better to begin with a relatively large dose lest the organisms become penicillin-fast and render subsequent treatment less satisfactory. In most cases doses in excess of 100,000 units daily are no more effective than smaller doses.

Penicillin may be used locally as well as systemically. A solution containing 25,000 units of penicillin in 100 cc. of water may be used to instil in cavities or to saturate packs applied to infected surfaces. The results of local application of penicillin are often dramatic, but the test of time has not as yet determined whether it is actually more effective when applied topically than when given systemically. The dry powder not only is irritating but also is expensive and has not been widely used for local application.

Penicillin is practically nontoxic. Occasionally mild febrile reactions and urticaria result from its administration, but these are thought not to be caused by the drug itself.[3] It has no untoward effect on the blood, kidneys, or liver, and no serious complications have been reported from its use.

Infection with the B. pyocyaneus does not respond favorably to treatment with sulfonamides, and it is doubtful whether penicillin therapy will prove more effective. Although this infection is often difficult to eradicate, saturation of the dressings with ½ per cent or 1 per cent acetic acid every four hours for a day or two will usually bring it under control.

Drainage. The provision of adequate drainage is the most important feature of the treatment of infection. If drainage is not provided, the infection will spread, systemic reaction will increase, healthy tissue will be destroyed, anaerobic organisms may gain a foothold, and chemotherapy will be ineffective.

Continuous soaks or wet dressings afford the best means of maintaining drainage. The constant moisture not only dilutes and washes away the pus but also prevents secretions from agglutinating the edges of the wound and from coagulating on the dressings to block drainage. Vaseline gauze packed loosely into a cavity is another effective means of maintaining drainage, but the surfaces when treated with vaseline are never so clean and healthy as when treated with continuous saline dressings.

When inadequately drained cavities are present or when a deep penetrating wound is infected, drainage may be provided by inserting a catheter into the depths of the wound and irrigating it every hour or two. Sometimes, if the wound is favorably located, a continuous drip system of irrigation may be set up.

The type of fluid used for irrigation is not so important as the frequency and regularity of the irrigations. Sulfanilamide powder suspended in a 1:500 aqueous azochloramid solution produces good results,

but plain saline will often clean up a bad infection in short order. Penicillin may be used when the cavity will hold the solution or when packing can be saturated with the solution.

If the infection does not respond to this type of therapy within three or four days, surgical revision of the wound should be considered. Often a minor procedure involving establishment of dependent drainage, removal of a piece of skin under which secretions are accumulating, or widening of a sinus draining a deep pocket will produce dramatic results. These revisions are less radical than those which were thought necessary before the advent of modern chemotherapy.

Immobilization. When wounded limbs are immobilized in plaster, healing takes place with remarkable freedom from spreading infection. If the casts are removed too early, and especially if the parts are not again immobilized, a flare-up of the infection may occur. For this reason it is well to immobilize a wounded extremity by splinting or encasing in plaster the joints both distal and proximal to the wound. The wound should be dressed infrequently, if at all, in the first two weeks. If no systemic reaction occurs and if the dressings do not become too foul, there is no indication for changing the dressings for two weeks or more. Wounds do better when left alone than when subjected to frequent dressings, provided, of course, that drainage is adequate.

Moist heat is of value in localizing infections, especially superficial infections which are pointing through the skin. Care must be taken to immobilize the part while heat is applied. If the infection is open and draining, heat is of less importance than moisture.

FOREIGN MATERIAL

Certain types of foreign material in a wound may interfere seriously with its healing, whereas others cause no untoward reaction. Some metals such as tantalum and to a lesser degree stainless steel lie inert in the tissues and cause no reaction even in the presence of infection. Tantalum plates have been reported to have remained securely in place and to have caused no foreign body reaction or drainage even when severe infection was present at the time they were introduced.[4]

Steel, brass, and lead cause relatively little tissue reaction. Aluminum, glass, and bits of wood and clothing, on the other hand, are irritating and cause a pronounced foreign body reaction. If fragments of nonirritating foreign bodies are small, they become encapsulated by fibrous tissue and may remain encysted in the body for years without causing any difficulty. One must think of these foreign bodies, encased

as they are in fibrous tissue, as little fibromas, not as jagged bits of metal. The reaction that they produce may be no more pronounced than that of a fibroma of comparable size.

Irritating foreign bodies never become encapsulated in fibrous tissue, because the reaction about them is so great that infection occurs, and abscesses or draining sinuses are formed. These foreign bodies must be removed.

Another kind of foreign body that is commonly seen in wounds is introduced by the surgeon in the form of suture material, drains, and strangulated tissue. Catgut is the most irritating of all suture materials, and plain catgut is more irritating than chromic. The very fact that plain catgut is absorbed more rapidly than chromic catgut indicates that it causes a greater reaction in the tissues, calls forth a greater number of phagocytes, and is therefore destroyed more rapidly than is the chromic. The incidence of infection will always be higher in wounds closed with catgut than in those closed with nonabsorbable and relatively nonirritative sutures. Silk is probably more irritating than cotton and certainly has a greater tendency to cause draining sinuses. The spaces between the fibers form pockets in which bacteria multiply and thrive. Fine cotton, no. 40 or finer, is less apt to cause persistent sinuses than is fine silk. In the presence of infection nothing larger than no. 60 cotton in single short-cut sutures should be used if the formation of sinuses is to be avoided.

Stainless steel wire, no. 32 or smaller, or fine tantalum wire is the best suture material for use in the presence of contamination. The nonirritating properties of these metals promote primary healing without infection, and if infection does occur, draining sinuses rarely follow.

Drains, whether they be of rubber, vaseline gauze, or plain gauze, act as foreign bodies and favor development of infection. Drainage with plain gauze is never indicated, because as soon as secretions from the wound coagulate upon it, dry gauze acts as a dam to obstruct further discharge of secretions. The only indication for plain gauze is as a pack to control hemorrhage.

Vaseline gauze and rubber drains keep the wound edges apart and allow secretions to escape. But they open the wound to contamination from the outside and lower its resistance to infection from within. One hopes that the pus in a wound will be attracted by some mysterious magnetism to the drain and escape to the surface. Too often the reverse is true, and contamination from the surface follows the drain to the depth

of the wound; then, when the tissue resistance is lowered by reaction around the drain, infection develops and spreads to involve the entire wound.

When wounds are clean enough to close, they do better when closed without drainage. When wounds are contaminated so badly that one hesitates to close them without a drain, it is better to pack them wide open. Exceptions to this rule occur when a hollow viscus or the liver has been injured, and when leakage of bile or gastrointestinal contents is anticipated. When rigid walled abscesses are opened, drains should be used. Drains are of value when bleeding is not completely controlled, but meticulous hemostasis produces better results.

Fat and fascia do not appear to cause much reaction in the tissues when they are strangulated by tight sutures, but necrotic muscle or glandular tissue acts as a foreign body and impairs healing. Sutures and ligatures should be placed so as to minimize strangulation of tissue, and all blood clots should be removed before a wound is closed.

Blood supply. Interference with the blood supply of a wound invariably results in poor healing. Every effort must be made to maintain an adequate blood supply lest infection become established and anaerobic organisms multiply in necrotic tissue.

When the blood supply of the bowel is interfered with or when circulation of an extremity is questionable, it is important to maintain blood pressure, hemoglobin level, and oxygenation of the blood so that whatever circulation remains in the affected part will function as efficiently as possible. Blood transfusion and oxygen therapy, when indicated, may make the difference between survival and gangrene of the affected part.

Application of tight bandages may impair circulation to such an extent that healing will be poor. In the lower leg or forearm the blood supply passes between the bones and is thereby protected from pressure, but tight bandages around a finger may hinder circulation. Pressure necrosis may occur in the skull and tibia where the bandage presses against the bone.

When a wound heals slowly over a long time, dense scar tissue is deposited at its base. As the scar contracts, the blood supply to the surface of the wound is impaired, and healing progresses very slowly. Epithelium may fail to grow on such a surface or may be extremely thin and susceptible to destruction by the slightest trauma. When wounds heal too slowly, it is often advisable to excise the scar tissue and to either close the wound or apply a skin graft.

REST

Immobilization of the wound is one of the most important features of treatment. It is hard to overemphasize the importance of rest in preventing the development and dissemination of infection. In addition, when the part is not placed at rest, mechanical factors prevent healing, as in the case of wounds over joints. We have all noticed the slowness with which wounds on the knuckles tend to heal and that these wounds break open repeatedly when the finger is moved. The healing process is mechanically disrupted by motion and may be retarded if rest is not provided.

PRESSURE DRESSINGS

When wound surfaces can be brought snugly together with a pressure dressing to eliminate dead space in which air, serum, or blood can accumulate, prompt healing is the rule. If pressure dressings are not applied, infection tends to occur in the dead space, and healing may be retarded. An efficient pressure dressing may be made of cotton waste secured with a woven elastic bandage or elastic adhesive tape.[5]

Pressure dressings not only obliterate dead space but also reduce edema around the wound. Tissues which are not edematous maintain a higher resistance to infection. Elevation of the part may help to reduce edema. Raw surfaces treated with pressure dressing are epithelized faster and with less infection than when pressure dressings are not applied.

VITAMIN C

Many studies on wound healing in the presence of vitamin deficiency have been made, but only a deficiency of vitamin C has been proved to retard wound healing.[6] Vitamin C deficiencies of sufficient severity to interfere with wound healing are rarely encountered. A deficiency of this vitamin should be considered when there is no other explanation for the failure of a wound to heal.

OTHER FACTORS INFLUENCING HEALING OF WOUNDS

It is likely that other vitamins as yet undiscovered play a part in wound healing. Certainly a deficiency in the serum proteins will produce edematous tissues, which heal poorly.[7] When serum proteins are low, every effort should be made to raise their level to normal.

The age of the patient does not appear to influence wound healing but debilitating disease does. Poor healing of wounds is often noted in jaundice, in advanced carcinoma, and when malaria complicates convalescence.

SUMMARY

The treatment of wounds must be based on sound knowledge of the physiology and pathology of the healing process. Wounds must be treated individually; no standard treatment can be defined.

Knowledge of the bacteriology of infections enables the physician to recognize types of wound infections, to judge their virulence, and to treat them. Sources of contamination include the instrument which inflicted the wound, ill guided attempts at emergency treatment, organisms from the nose and throat of the patient or his attendants and from the air. Established infections may be treated with the sulfonamides or penicillin, by immobilization, and by pressure dressings, which obliterate dead spaces, approximate the tissues, and allow normal healing to take place. Continuous soaks or wet dressings afford the best means of maintaining drainage, which is the most important feature of treatment of infection.

Nonirritating foreign bodies, if the fragments are small, may remain encysted within the body without causing difficulty: Irritating foreign bodies must be removed. It must be remembered that a foreign body is introduced into the wound by the surgeon in the form of suture material, drains, and strangulated tissue.

Interference with good blood supply invariably results in poor healing. Although only a deficiency of vitamin C has been proved to retard wound healing, it is likely that a deficiency in the serum proteins or in other vitamins as yet undiscovered or the presence of a debilitating disease also plays an important part.

Immobilization of the wound is of prime importance in preventing the development and dissemination of infection and in eliminating mechanical factors which prevent healing.

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RETROPERITONEAL TUMOR

Fibrosarcoma of the Adrenal

Report of a Case

CHARLES C. HIGGINS, M.D.

In recent years many cases of adrenal tumors originating in the cortex or medullary portion of the gland have been reported. In the presence of an abdominal mass and clinical signs of adrenal hyperactivity a tentative diagnosis of adrenal tumor may be made. Nonrenal retroperitoneal tumors may be (1) parietal retroperitoneal tumors arising from the walls and mesothelial structures of the retroperitoneal space or (2) unattached retroperitoneal tumors usually arising from the mesonephron or the gonad. A case is reported in which a retroperitoneal tumor, probably arising from the adrenal gland, displaced the gallbladder to the left upper abdominal quadrant and the right kidney below the left kidney. The viscera, gallbladder, and right kidney returned to their normal positions after the tumor was removed. The site of origin was difficult to determine from the gross and microscopic study of the tumor.

CASE REPORT

A woman, aged 74, was admitted to the clinic on December 11, 1944 complaining of a painful mass in the right side of the abdomen. Symptoms began one year previously, when after an attack of pneumonia pain occurred in the right kidney region. She observed the presence of a mass, which progressively enlarged until it occupied the entire right half of the abdomen. During the past year her weight dropped from 173 to 140 pounds. She was forced to go to bed frequently because of weakness. The patient had no other complaints.

Physical examination revealed a fairly well nourished woman. The size and shape of the abdomen immediately attracted attention. Temperature was 98.6 F., pulse rate 80 per minute, respirations 20 per minute, and the blood pressure 185 mm. of mercury systolic and 105 mm. of mercury diastolic. A large firm mass occupied the entire right side of the abdomen and was slightly movable and somewhat tender to deep pressure. The mass extended from under the ribs to below the anterosuperior spine and was smooth with the exception of two large nodules on the anterior surface.

Roentgenologic studies. An initial roentgenogram revealed a large laminated calculus in the left upper abdominal quadrant and a homogeneous, fairly dense shadow on the right side of the abdomen. No gas shadows were present in this area.

A retrograde pyelogram showed the left kidney at a level lower than normal, the upper pole being at the second lumbar vertebra (fig. 1). The right ureter crossed the sacrum and entered the right kidney, which lay below the left. A large mass occupying the right side of the abdomen had displaced the bowel to the left and into the pelvis (fig. 2a). It could not be stated with certainty whether the two kidneys on the left were joined with anomalous ureters or whether the right kidney was displaced far to the left by the enormous mass.

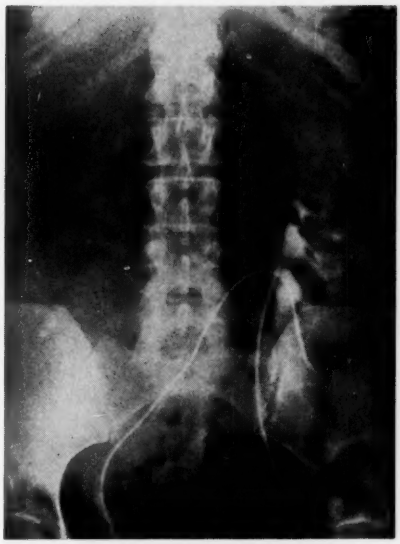

FIG. 1 Retrograde pyelogram showing left kidney at lower than normal level and right ureter crossing sacrum and entering right kidney, which has been displaced below the left.

On roentgenologic examination the transverse and ascending portions of the colon were displaced downward and toward the midline by the large right abdominal mass, and the lower pole of the stomach was three inches below the iliac crest (figs. 2b and c). The mediastinum and aorta were normal, and the heart was normal in size, shape, and position. The left lung was normal, but the right lung showed exudative and calcific infiltration, and a diagnosis was made of probable bronchitis.

The large mass, filling the right side of the abdomen and extending across the spine, had displaced the gallbladder, stomach, and intestine far to the left and probably had displaced the right kidney to its position below the left kidney. It did not seem unreasonable to assume that the lesion was an unusually large retroperitoneal sarcoma.

Laboratory Data

Urine	Blood
Specific gravity—1.020	Hemoglobin—85 per cent
Alkaline reaction	Red blood cells—4,130,000
Albumin—1 plus	White blood cells—6500
Sugar—none	Urea—24 mg. per 100 cc.
Microscopic examination—occasional white blood cell	Sugar—116 mg. per 100 cc.
	Wassermann reaction—negative

Operation (December 15, 1944). Through the usual kidney incision a large retroperitoneal tumor was exposed. It was mobilized with considerable difficulty and

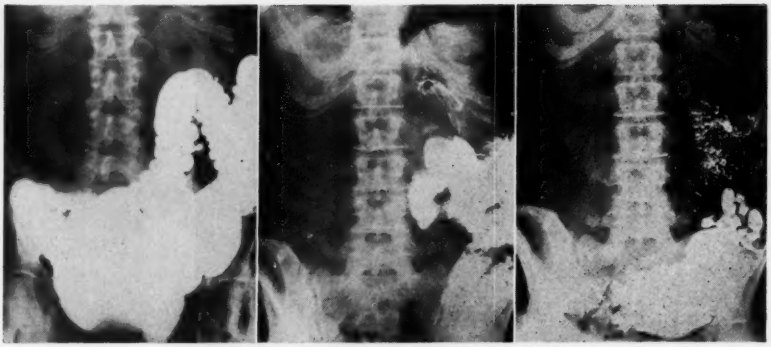

FIG. 2(a) Roentgenogram showing transverse and ascending portions of the colon, displaced downward and toward the midline by the large right abdominal mass, and calculus in gallbladder, also displaced to the left.

(b) Roentgenogram after barium meal. Stomach is three inches below iliac crest. Jejunum and duodenum are filled with barium.

(c) Roentgenogram after barium meal. Barium fills small bowel. Calculus in displaced gallbladder.

was quite adherent in the region of the aorta and vena cava. By sharp dissection the mass was freed from these structures and removed. Two cigaret drains were inserted, and the wound was closed.

The patient was discharged from the hospital January 4, 1945 in satisfactory condition.

Pathologic report*

A. Gross. The specimen is a large ovoid mass weighing 2250 Gm. and measuring 19 by 14 by 12 cm. The exterior is formed by a gray, partially opaque, slightly roughened capsule to which are adherent small masses of adipose tissue and one cordlike strand. The capsule is mottled with areas of red, yellow, and blue-gray. Parallel sections show bulging, moist, and irregularly, coarsely, and indistinctly lobulated cut surfaces formed in variegated tissue, which is mainly pinkish gray. Scattered through it are slightly protruding, indistinctly delimited, nodular masses, which are more gray and opaque than surrounding reddish gray translucent tissue. There are small to large portions which are yellow, opaque, and friable, and other portions which are softer, semitranslucent, and greenish gray. There are also roughly and smoothly lined cysts up to 2.7 cm. in maximum diameter containing clear yellow and greenish yellow fluid. In and immediately beneath the capsule are several elongated patches of orange-yellow opaque tissue suggestive of adrenal cortex. Sections through these portions show a thin subcapsular layer of orange-yellow opaque tissue up to 1 mm. thick.

B. Microscopic. Numerous sections show a well encapsulated mass with portions of compressed adrenal cortex in parts of the capsule. The mass is varied in structure but in general shows about equal amounts of cells and intercellular fibrillar material. The cells, moderately large, vary greatly in shape. Some are fusiform, arranged in bundles,

* This report was made by Dr. C. M. Blumenfeld, Department of Pathology, University Hospitals, Cleveland.

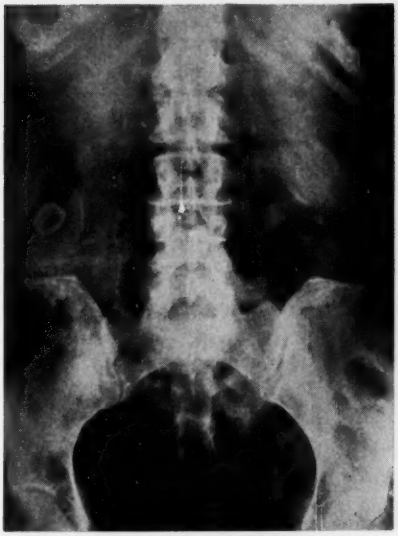

FIG. 3 Postoperative roentgenogram showing gallbladder and right kidney returned to normal position.

but more are arranged in no regular pattern, their shape being obviously pleomorphic, being round, oval, polygonal, stellate, and irregular. Some sections show cells closely packed without visible intercellular substance, forming short, irregular, in part anastomosing trabeculae, which tend to center about small thin-walled vascular spaces, from which they are separated by pale eosinophilic or fibrillar material. In various portions of the mass, but particularly in the more richly cellular part, there are occasional bizarre giant cells, round, oval, or irregular, with multiple nuclei, sometimes centrally clustered, sometimes arranged in a complete or incomplete peripheral ring. In general the nuclei are slightly to severely hyperchromatic and composed of a coarse network of chromatin. Only occasional large nucleoli are seen. The cytoplasm is eosinophilic and varies from homogeneous to commonly irregularly vacuolar and granular. There is a moderate number of normal and abnormal mitotic figures. Vascularization varies from poor to moderate and is principally by vessels of sinusoidal type with large lumens and walls of endothelium only. In some places vascular spaces are formed by tumor cells. Large portions show degeneration and necrosis. Where portions of the periphery of the mass are included, there is a thick capsule of poorly cellular, dense, coarse, collagenous, fibrous tissue, partially hyalinized. Selected parts include portions of adrenal cortex showing the usual vacuolated cells in cordlike arrangement compressed in a pattern tangential to the mass. In most places the cortical spaces are separated from the tumor by capsular tissue, but in a few, isolated nests of cortical cells approximate the neoplastic cells. Van Gieson's preparations show abundant material staining like collagen, in part disposed as coarse bundles between groups of cells and in part as fine fibers intimately related to and placed between individual cells. In general

mucicarmine preparations are not positive, but in some parts, particularly where degeneration and necrosis are seen, fine and irregular fibrils stain moderately deep red.

Bodian preparations of two selected portions show a few, short, isolated, impregnated fibrils, which are not related to the tumor cells but lie free in the intercellular substance. In the regular preparation a selected portion shows bundles having the appearance of smooth muscle cells in cross section; a van Gieson preparation shows these bundles stained yellow. Tumor is located on one side of these bundles and capsular tissue on the other side.

C. Comment. Lack of organoid differentiation, pleomorphism of cells, and moderate numbers of normal and abnormal mitotic figures indicate that this is a malignant tumor. Presence of compressed adrenal cortex in portions of the capsule indicates an intimate relation with the adrenal gland. However, the tumor may have arisen from the retroperitoneal tissue and as it expanded may have caused compression atrophy and inclusion of the adrenal gland in its capsule. Thus, although intimate relation of the tumor and adrenal gland strongly suggests adrenal origin, retroperitoneal origin cannot be finally excluded. The abundance of collagen, as demonstrated by van Gieson's preparation, its wide distribution, and its intimate relation to the tumor cells indicate that it is a product of them and not merely stroma. In appearance the cells differ from fibroblasts seen in average fibrosarcoma, and many portions of the tumor show a perithelio-matous arrangement unlike that seen in ordinary fibrosarcoma. The short segments of intercellular fibrils impregnated by Bodian preparation cannot be construed as indicating that the tumor is of neural origin. The fibrils may be nerves of the tumor rather than products of tumor cells. The bundles of smooth muscle are like those seen in the wall and major branches of the adrenal vein. The presence in one section of such smooth muscle bundles on one side and of tumor capsule on the other side suggests that the tumor may have grown into and in a large part obliterated the wall of either the main central adrenal vein or a tributary.

In conclusion it may be stated that morphologic evidence favors adrenal origin but does not exclude the possibility of retroperitoneal origin. Neural origin also cannot be excluded, but demonstrated features are consistent only with a diagnosis of fibrosarcoma, adrenal cortex being derived from mesoderm (mesothelium). It is also impossible to exclude origin from adrenal cortex with assumption by the altered tumor cells of fibroblastic potency.

Postoperative roentgenograms demonstrated a large gallbladder calculus on the right side of the abdomen above the crest of the ilium (fig. 3). The intravenous urogram showed prompt function from both kidneys, which lay low with the lower poles at the level of the iliac crests. The right kidney had shifted to the right. The bladder appeared normal.

SUMMARY

In this case a large retroperitoneal tumor probably arising from the adrenal gland had attained sufficient size to displace the gallbladder to the left side of the abdomen and the right kidney to a position below the left kidney. Great displacement of the other viscera was evident. Exploratory surgery is valuable when such a lesion appears clinically to be inoperable. As is demonstrated in this case classification of non-renal retroperitoneal tumors from the gross and microscopic study of the tumor is difficult.

REMOVAL OF BROKEN KNIFE BLADE FROM SPINAL CANAL

Report of a Case

W. JAMES GARDNER, M.D.

In the absence of infection the presence of a metallic foreign body in the tissues may be of little clinical significance. This, however, is not always true. The following case is reported because it demonstrates conclusively that a metallic foreign body can cause progressive damage to adjacent nerve tissue. The foreign body was a chrome-plated steel knife blade with a nick exposing the steel on that part of the blade which lay within the spinal cord. Corrosion occurred at this site. Pain was the first irritative symptom and began one month after introduction of the foreign body. Signs of cord damage progressed rapidly from the twelfth to the fourteenth month and began to subside within five days after the blade's removal.

CASE REPORT

A white man, aged 37, was first examined on October 11, 1944 with complaints of weakness in the legs, numbness from the waist down, and pains about the lower chest. While employed as a bus driver in October 1943 he was attacked by a passenger. As he ducked under his assailant's arm, he received a blow on the back and dropped to the floor paralyzed from the waist down. He was taken to a hospital, and his wife was told the paralysis was caused by hysteria.

Roentgenologic examination of the spine ten days after the accident was said to be normal. At the end of fifteen days a slow gradual return of function began and continued for three months, after which numbness and weakness remained static. After the injury the patient had constipation, hesitancy and urgency of urination, and complete impotence. A month after the accident he developed gradually increasing pains radiating from his spine forward about the lower borders of the ribs. The patient was examined by a neurologist six months after injury and was told that he had a stab wound of the spinal cord. Because of disability of the lower extremities he was advised to get a sedentary job and became a clerk in a steel plant. He sought further advice because of increasing pain.

Examination revealed a small transverse scar 2 cm. in length just left of the midline below the tip of the ninth dorsal spinous process. At the time of injury this wound was apparently considered a superficial laceration. The gait was very spastic, especially movement of the right leg. The abdominal reflexes were active and equal. The patellar and Achilles tendon reflexes were hyperactive. Babinski reflex and ankle clonus were present on the right. There was almost complete analgesia of the left lower extremity up to the eleventh dorsal dermatome, and slight hypalgesia in a corresponding distribution on the right. Thermal perception was similarly disturbed over a similar area. Perception of light touch was less impaired. Roentgenologic examination of the lower dorsal spine showed the broken end of a knife blade 6 cm. in length passing between the lamina of the ninth and the tenth dorsal vertebra. The tip was buried in the posterior

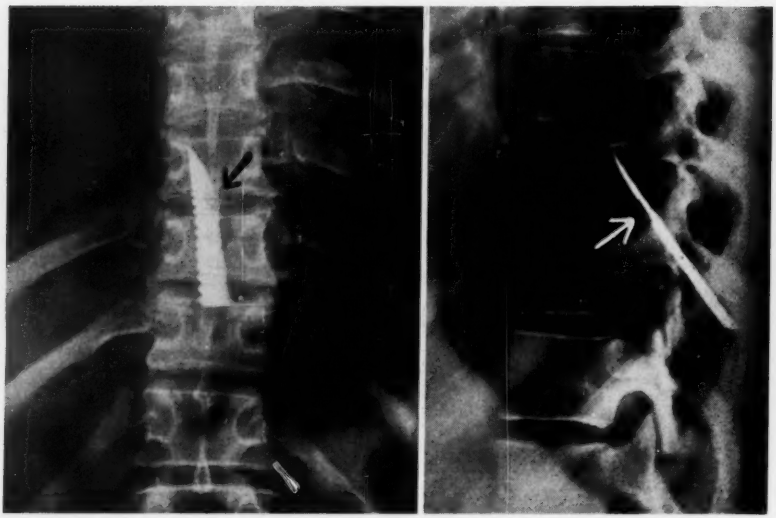

FIGURE 1. Roentgenograms showing position of blade. Arrows point to location of nick within spinal canal.

portion of the body of the ninth dorsal vertebra (figure 1). The diagnoses were stab wound of the spinal cord causing Brown-Sequard's paralysis and foreign body in the spinal canal.

The patient was informed of the presence of the foreign body and was advised to have it removed if paralysis increased. Immediate operation was not advised because of the risk of aggravation of symptoms, which might accompany the trauma of removal. He was fitted with a spinal brace and advised to limit his activity and to sleep on a firm bed.

The patient was admitted to the hospital two months later. He had increasing difficulty in walking during the past five weeks and for three weeks had been unable to walk alone. He had increasing constipation as well as frequency, urgency, and occasional loss of urinary control. Examination revealed virtually complete paralysis of both legs, a bilateral Babinski response, and more pronounced sensory findings than on previous study. Bladder function appeared to be automatic.

The patient was operated upon on December 11, 1944 under pentothal anesthesia. The broken knife blade was found passing forward between the ninth and the tenth spinous process. The eighth, ninth, and tenth spinous processes and their laminae were removed. After exposing the extraspinal portion, the knife blade was found to be loose and freely movable and was withdrawn readily from the spinal canal. The scar in the dura and cord was freed by incising the dura surrounding it. Some constriction of the spinal cord by scar tissue contraction of the dura was evident. The knife blade had entered the posterior aspect of the spinal cord about 3 mm. to the left of the midline and had passed diagonally forward and to the right. Whether the blade had entirely severed

the right lateral aspect of the cord was uncertain, but it appeared probable because of the width of the blade. Some of the scarred dura was removed for microscopic study. The wound was closed with several tiers of interrupted black silk sutures.

The knife blade was sharp, of chrome-plated steel, 6 cm. in length and 11 mm. in its greatest width, and had on its posterior edge a series of saw-toothed serrations apparently designed for scaling fish. A thumbnail groove indicated that it was a clasp knife. On the cutting edge 1.5 cm. from the point and corresponding to the nick shown on the roentgen film was an area of corrosion measuring 7 by 4 by 1.5 mm. This rusty portion of the blade had been embedded in the spinal cord. The broken end of the blade, which had been buried in the muscles outside the spinal canal, showed virtually no corrosion, although more of the steel was exposed here than at the nick on the cutting edge.

The patient's postoperative course was uneventful. Munro tidal drainage was carried out until the eighth postoperative day when he began to void voluntarily. When discharged on the twelfth postoperative day, he was able to walk, and his pain was relieved. Two months after operation the patient was able to walk without support although with considerable spasticity. The sensory picture was unchanged. He voided with some difficulty and still had complete impotence. He was beginning to have some recurrence of root pain in the distribution of the right ninth dorsal dermatome.

COMMENT

A common mistake of clinicians in diagnosing lesions of the spinal cord is to place the lesion too low in the vertebral column. This is largely due to the fact that nerve roots ascend within the spinal canal to enter the cord at a level higher than the corresponding vertebrae. Thus it is not uncommon for a roentgenogram of the lumbar spine to be ordered in a case of spastic paraplegia, when the spasticity alone is positive proof that the lesion is above the lumbar level. In this case roentgenologic examination at the time of the accident was probably made at too low a level, and therefore the foreign body was not discovered. The neurologist who examined the patient six months later was told that the initial examination was negative and did not request additional films. Twelve months after the accident this omission was almost repeated.

It seems unlikely that pressure due to the increasing bulk of the rusting foreign body could have been responsible for the progressive damage to the cord. The fact that the blade was not closely invested by surrounding tissue suggests intolerance on the part of the host to the metals of the knife blade. It is interesting to speculate why the exposed portion of steel within the spinal cord oxidized more rapidly than that portion buried in the spinal muscles.

THE EFFECT OF 3,3′-METHYLENE-*BIS*-(4-HYDROXYCOUMARIN) (DICUMAROL) ON THE PROTHROMBIN AND COAGULATION TIMES OF BLOOD

THREE YEAR SUMMARY

F. A. LeFEVRE, M.D.

In July 1942 the results of the use of dicumarol in 23 patients were reported.[1] Since that time the drug has been administered to 70 additional patients, making a total of 93. After the article of Butt, Allen, and Bollman[2] on the administration of dicumarol in man numerous articles appeared. These were summarized by Gefter, Kramer, and Reinhold[3] in 1944 in a comprehensive review of the literature and a report of 30 cases of thromboembolic disease in which the preparation was used.

Clinical conditions for which dicumarol was administered. The table classifies conditions for which dicumarol was administered at the Cleveland Clinic up to March 1945. The largest group consisted of acute superficial thrombophlebitis. These cases were differentiated from those of deep thrombophlebitis because the degree of clinical response seemed to vary. The second largest group consisted of cases of retinal thrombosis involving the vein or artery. The remaining cases were of postoperative pulmonary embolus, thromboangiitis obliterans, coronary thrombosis with infarction of the myocardium, and peripheral arterial thrombosis, either secondary to heart disease or caused by arteriosclerosis obliterans (table).

TABLE

Diagnosis	No. of Cases
Acute superficial thrombophlebitis	28
Deep thrombophlebitis	10
Thromboangiitis obliterans	8
Coronary thrombosis	7*
Arteriosclerosis obliterans with thrombosis	7
Subacute bacterial endocarditis	6
Thrombosis of retinal vein	20
Thrombosis of retinal artery	3
Postoperative pulmonary embolism	4
TOTAL	93

* Three treated at another hospital.

Method of administration. The administration of dicumarol presents an interesting but difficult problem. Various methods have been proposed. Meyer, Bingham, and Pohle[4] recommended an initial dose of 5 mg. per kilogram body weight followed by $\frac{1}{5}$ to 1 mg. per kilogram daily. Among others Gefter, Kramer, and Reinhold[5] used this method in their series of 30 cases. My clinical experience, however, showed that this method of administration was difficult to control, inasmuch as the effect of dicumarol is cumulative, and maximum changes in the prothrombin time usually do not occur until forty-eight hours after administration. In this series the only toxic effects including hematuria followed the continuous daily administration of dicumarol. Although the method as described appears to be ideal, I found the complications attendant to its use excessive.

I have not been able to work out accurately any method of administration based on body weight. Moreover, in the oral administration of any preparation allowance must be made for the numerous variable factors that frequently make any measurable constant result impossible to estimate. This seems to be especially true of the oral administration of dicumarol.

It did seem possible, however, to administer this drug by certain methods whereby an average result could be anticipated: Adults weighing under 150 pounds received 250 mg. orally the first day and 100 mg. on the second and third days. Those weighing over 150 pounds received 300 mg. orally the first day and 150 mg. on the second and third days. The drug was then discontinued. The prothrombin time was estimated before administering dicumarol and every other day thereafter. An attempt was made to elevate the prothrombin time to 30 to 45 seconds. Levels below 30 seconds were relatively ineffective, and although levels above 45 seconds rarely produced hematuria, the results were not commensurate with the increase.

Usually the prothrombin time rose promptly between twenty-four and forty-eight hours, the peak being reached from the fifth to the eighth day, and returned to normal from the tenth to the twelfth day. If the patient responded to the drug according to this pattern and if no toxic signs appeared, a follow-up dose of 100 to 150 mg. was given, depending upon the body weight, provided that further elevation of the prothrombin time was desired. This small dose usually resulted in an elevation lasting from five to six days, whereupon the dose was repeated if necessary. Since a corresponding rise in the coagulation time does not always occur, the more consistent effect upon the prothrombin time determine its use as an index. In these studies the Lee and White method for estimating the prothrombin time was used.

COMMENT

It has been definitely demonstrated that dicumarol increases the prothrombin time in man. The effect, however, is not always constant in persons of similar ages and weights suffering from the same disease. Because of possible deviations and the need for both clinical and laboratory observations, dicumarol is not a satisfactory preparation to be used in general office practice. All patients receiving the drug should be hospitalized and the indications for its administration carefully studied.

Indications and contraindications. The use of dicumarol should be considered in any condition showing acute arterial or venous thrombosis. The use of dicumarol is contraindicated in subacute bacterial endocarditis. Two of six patients treated with dicumarol in conjunction with other methods of therapy died in the hospital. In one, death was found to be due to cerebral hemorrhage, and in the other, to a pulmonary embolus. In neither patient did the prothrombin time exceed 35 seconds. It is fair to assume that cerebral hemorrhage as the cause of death in the first patient was related to the increased prothrombin time. In the second patient the increased prothrombin time did not prevent the pulmonary accident. In general, patients suffering from subacute bacterial endocarditis have fluctuations in prothrombin time with a tendency toward abnormal bleeding, and therefore the drug should not be used in treatment.

Dicumarol is also contraindicated in the presence of any chronic liver or renal disease, especially when there is a deficiency of vitamin K or demonstrable decrease in urinary function. Blood dyscrasias with bleeding tendencies and any existing prothrombin deficiency, such as may occur with jaundice or nutritional disease, are contraindications. The drug should not be used in any open ulceration because local hemorrhage may readily occur.

Toxicity. The commonest toxic effect of dicumarol is hematuria. This occurred in five patients. In two, whole blood given intravenously promptly checked the bleeding. In three cases in which no therapy was given the hematuria cleared up spontaneously. I have not used vitamin K intravenously in large doses to lower the prothrombin time. Cromer and Barker[6] reported beneficial results from its use in treating excessive hypoprothrombinemia induced by dicumarol. The only other hemorrhagic manifestation was the one case of subacute bacterial endocarditis terminating with cerebral hemorrhage. At postmortem examination no evidence of liver damage was observed.

No unusual effects were noted on the hemoglobin, erythrocyte count, leukocyte count, or urine. In the series reported by Gefter[3] no unusual effects were noted in other laboratory investigations.

Results. In this series dicumarol was used chiefly in cases of superficial acute thrombophlebitis, and when used in the early stages, during the first two weeks, the course of the disease seemed to be moderately checked. In deep thrombophlebitis or phlebothrombosis dicumarol did not seem to produce any beneficial clinical effects. In thrombosis of the retinal veins improvement in vision was noted in 50 per cent of the patients. In the remaining 50 per cent none of the eyes were enucleated owing to secondary glaucoma. In coronary thrombosis and thrombosis of the peripheral arterial circulation recovery was satisfactory, although it is not possible to ascertain the course of the disease in these patients if dicumarol had not been used. Results were compared with those of other methods of treatment in patients with similar clinical and laboratory findings.

In a group of patients suffering from postoperative pulmonary embolism no deaths occurred. In April 1943 a large series of cases was reported by the Mayo Clinic in which dicumarol was given routinely to patients having abdominal hysterectomies, and the incidence of pulmonary embolism was greatly reduced.[5] It has been noted that patients with an increased clot retraction time have a higher incidence of postoperative pulmonary embolism than those showing a normal clot retraction time. In this group, therefore, the prophylactic use of dicumarol might be advisable.

My experience with dicumarol in the treatment of thromboangiitis obliterans has been limited but does not indicate that this drug is an effective part of treatment.

Advantages. The cost of dicumarol is exceptionally low, and it tends to have an effective and prolonged action when given orally, which makes intravenous therapy unnecessary. In these respects it is probably more advantageous to use than heparin. On the other hand, dicumarol is not effective for twenty-four to forty-eight hours, and if immediate action is desired, heparin should be given intravenously. When combined treatment is indicated, heparin is administered intravenously at the outset, and dicumarol given orally at the same time. When dicumarol becomes effective at the end of the first or second day, heparin may be discontinued. It may be noted here that heparin has a more constant effect on the coagulation time than it does on the prothrombin time, whereas the opposite is true of dicumarol.

SUMMARY

In 93 cases of thromboembolic disease the effects of dicumarol as a part of treatment were observed from clinical and laboratory standpoints. Dicumarol is effective in increasing the prothrombin time of the blood; however, this effect is not constant, and no specific or routine method of administration can be proposed at present. The drug should be used cautiously, and the patient to whom it is administered should be hospitalized for careful observation.

The dicumarol was supplied by Eli Lilly and Co., Indianapolis, Ind.

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